Importance and Contribution of Community, Social, and Healthcare Risk Factors for Hepatitis C Infection in Pakistan

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Abstract. Pakistan has a high prevalence of hepatitis C virus (HCV) infection, estimated at 4.9% (2,290/46,843) in the 2007 national HCV seroprevalence survey. We used data from this survey to assess the importance of risk factor associations with HCV prevalence in Pakistan. Exposures were grouped as community (going to the barbers, sharing smoking equipment, having an ear/nose piercing, tattoo, or acupuncture), healthcare (ever having hemodialysis, blood transfusion, or ≥ 5 injections in the last year), demographic (marital status and age), and socio-economic (illiterate or laborer). We used mutually adjusted multivariable regression analysis, stratified by sex, to determine associations with HCV infection, their population attributable fraction, and how risk of infection accumulates with multiple exposures. Strength of associations was assessed using adjusted odds ratios (aOR). Community [aOR females 1.5 (95% confidence interval [CI]: 1.2, 1.8); males 1.2 (1.1, 1.4)] and healthcare [females 1.4 (1.2, 1.6); males 1.2 (1.1, 1.4)] exposures, low socio-economic status [females 1.6 (1.3, 1.80); males 1.3 (1.2, 1.5)], and marriage [females 1.5 (1.2, 1.9); males 1.4 (1.1, 1.8)] were associated with increased HCV infection. Among married women, the number of children was associated with an increase in HCV infection; linear trend aOR per child 1.06 (1.01, 1.11). Fewer infections could be attributed to healthcare exposures (females 13%; males 6%) than to community exposures (females 25%; males 9%). Prevalence increased from 3% to 10% when cumulative exposures increased from 1 to ≥ 4 [aOR per additional exposure for females 1.5 (1.4, 1.6); males 1.2 (1.2, 1.3)]. A combination of community, healthcare, and other factors appear to drive the Pakistan HCV epidemic, highlighting the need for a comprehensive array of prevention strategies.

INTRODUCTION

Hepatitis C virus (HCV) infection is a blood-borne pathogen that causes considerable morbidity and mortality globally.^{1,2} Recent estimates suggest that there are an estimated 80 million people living with HCV infection globally.³ In developed countries, the primary mode of HCV transmission is injection drug use,^{4,5} but most of the HCV burden is concentrated in lower income and middle income countries,^{1,2} where most transmission is thought to be due to nonsterile healthcare and community practices.^{6–11} Healthcare practices associated with HCV-related risk include injections for medical purposes, blood transfusion, surgery, dental procedures, and receipt of intravenous infusions.^{10,12–15} Community exposures found to be associated with HCV infection include barbering, tattooing, and ear and nose piercing.^{9,12,16,17}

The prevalence of HCV infection in most countries is low ($< 1\%$), but exceeds 4% in at least 12 countries including Egypt, Georgia, Nigeria, Russia, and Pakistan.^{3,13,18} The burden of HCV is also concentrated, with about half (over 50 million) of all exposed adults (anti-HCV positive) living in six countries: Egypt, Pakistan, India, China, Russia, and Nigeria.³

Since the World Health Organization (WHO) released its Global Health Strategy for eliminating viral hepatitis,¹⁹ there has been substantial interest in gaining a better understanding of how much HCV treatment scale-up is needed to reduce the transmission of HCV to low levels, especially in the highest prevalence settings such as Egypt, Georgia, and

Pakistan.^{20,21} However, to achieve large reductions in HCV transmission, it is also crucial to tackle the underlying risk factors that drive HCV transmission. In addition, to effectively scale-up treatment it is also important to understand how to optimally target HCV testing interventions to minimize costs. This is especially true for countries with a large burden of HCV such as Pakistan, where there are an estimated 9 million people affected,¹⁸ and healthcare expenditure only makes up 0.9% of gross domestic product (compared with 10.0% across the EU and 17.1% in USA²²). Understanding what risk factors and markers are predictive of HCV infection (e.g., testing anti-HCV positive on a screening assay) could inform efficient, targeted screening recommendations that could reduce costs.

Recognized interventions for reducing HCV transmission among people who inject drugs (PWID) include opiate substitution therapy^{23–27} and needle and syringe provision,^{25,28} whereas modeling suggests that HCV treatment as prevention may also be an effective intervention.^{29,30} Beyond PWID, the focus globally for reducing HCV transmission has centered on behavior change strategies (by WHO and the Safe Injection Global Network [SIGN]) to minimize unsafe injections.³¹ During 2000 to 2010, these strategies succeeded in reducing reuse of injection equipment from 39.6% to 5.5% in the 71 countries assisted by WHO (including Pakistan).³² Recently, WHO launched a new global policy on injection safety to be piloted in a number of countries.³³

In Pakistan, since 2005 a number of major hepatitis prevention and control programs^{34,35} have focused on ensuring safe blood transfusions, improving disposal of syringes, increasing public awareness, and educating healthcare professionals and barbers^{36–38}; but unfortunately, the effectiveness of these interventions in reducing HCV transmission in Pakistan is unknown.

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In 2007, a large ($N = 46,843$) national seroprevalence survey for HCV was carried out in Pakistan and found anti-HCV prevalence of 4.9% overall, 6.7% among adults (aged ≥ 16 years), which did not differ by sex.¹⁸ HCV infection prevalence was higher in the more populous provinces of Punjab (6.7%) and Sindh (5.0%), than in the less populated provinces of North-West Frontier (1.5%) and Baluchistan (1.1%). Previous analyses using this dataset have only considered univariate associations with HCV seroprevalence meaning that these associations did not take into account the effects of other variables and were open to issues of confounding. In this report, we expand on these previous unadjusted analyses by undertaking a multivariable analysis of associations with exposures and risk factors for HCV infection. We estimate that the population attributable fraction (PAF) of HCV is due to grouped community or healthcare exposures and risk factors. The PAF assesses the proportion of prevalent infections attributable to different exposures and depends both on the strength of association with HCV infection and the population prevalence of the risk factor. We also assess the cumulative effect of multiple exposures on lifetime HCV-related risk.

MATERIALS AND METHODS

Data collection. Survey methods and sampling frame have been described previously.¹⁸ Briefly, the survey was conducted in four provinces with households drawn from primary sampling units, 138 urban and 212 rural. Included subjects gave consent to being tested.

Demographic information. Age, sex, marital status (never married, married, or divorced/separated/widowed), and relationship with the survey responder were collected for all members of the household. Each person and household had a unique identifier and was labeled with the district and province. If a person's age was missing they were removed from the analysis. Age was grouped as 20–29, 30–39, 40–49, and 50–59 years. The district was used to categorize households as urban or rural.

Outcome variable. Sample testing for HCV was carried out using the rapid Advanced Quality One Step HCV Test (Bionike Inc.) system, which is estimated to have a sensitivity of 97.1% [95% confidence interval (CI): 89.8–99.6%] and specificity of 96.3% (92.5–98.5%).³⁹ Participants were only tested for antibodies to HCV (anti-HCV), not active infection.

Exposures and risk factors collected in the survey. Data were collected on whether participants had ever received hemodialysis, blood transfusion, had a history of surgery, had a family history of HCV infection, practiced matam (ranges from ceremonial chest beating to self-flagellation with implements such as chains and blades),^{40,41} had visited a dentist, had visited a barber, shared a toothbrush, shared smoking equipment, had either a tattoo or acupuncture, had either an ear or nose piercing. The number of medical injections received in the last year (0, 1–4, 5–10, > 10), and the type of syringe used (none, new disposable, reused syringe, don't know) was recorded. Occupation was dichotomized as laborer or not, education was dichotomized as illiterate or not.

Derived variables—grouped exposures and risk factors (S-ES, healthcare, and community). Risk factors and exposures that are surrogates for risk factors (e.g., literacy as an indicator of socio-economic status [S-ES]) were grouped as S-ES, healthcare risk, and community risk exposures. S-ES for all

individuals was defined using data on the survey responder (assumed to be the head of the household). An individual was defined to have low S-ES if the head of the household was either a laborer or illiterate. Risk because of healthcare exposures was high if the person had previously had hemodialysis, a blood transfusion, or ≥ 5 injections in the last year. Lower numbers of yearly injections were not included as a healthcare risk exposure because 77% of the population reported at least one injection in the last year. Community exposures included going to the barber, sharing smoking equipment, having an ear or nose piercing, or having a tattoo or acupuncture. For each of the healthcare and community grouped risk/exposure variables, we counted the number of exposures and categorized them as 0, 1, or ≥ 2 risk factors. We also counted the total number of exposures (0, 1, 2, 3, 4, or ≥ 5 risk factors).

We also hypothesized that unsafe childbirth practices could be a risk factor for HCV acquisition in adult females. Although the survey did not directly ask respondents about their number of childbirths, it did list each household member and what their relationship was to the head of the household. Therefore, for females aged 20–59, who described themselves as wife or head of household, and who identified themselves as married, the number of childbirths (0, 1, 2, 3, 4, ≥ 5 children) was estimated by counting the number of children in the household described as sons or daughters. We did not estimate the number of childbirths for older females because of the increased likelihood that some of their children would have left home. Age was grouped as 20–29, 30–39, 40–49, and 50–59 years in this analysis.

Statistical analysis. We tabulated HCV prevalence for the country, and by province and district. We also tabulated prevalence by age (0–19, 20–29, and ≥ 30 years) and sex and cross-tabulated with the prevalence of risk factors/exposures for HCV acquisition.

Association of exposures and risk factors with HCV. We used logistic regression to estimate the unadjusted and mutually adjusted odds ratio (OR) (with 95% CI) for HCV infection for each exposure. Separate models were estimated for each age group (0–19, 20–29, and ≥ 30 years) and sex to see how associations varied across these groups. We also estimated the association of age with HCV prevalence by fitting separate models for males and females that included age as a covariate. Robust standard errors accounted for clustering by household.

To assess which of social, healthcare, or community interventions might have more impact on HCV risk/exposure, we grouped variables into these domains and reestimated mutually adjusted sex-specific models which were also adjusted for province, age, and marital status. We performed a separate analysis splitting the derived group variables into their individual components. We examined whether age modified the association of exposures with HCV infection by including the interaction with age as a continuous variable. We defined PAF (Equation 1) as the proportional reduction in HCV that would occur if the risk factor were reduced to no exposure and calculated this for each of the three factor domains.⁴² We examined the relationship between HCV prevalence and the total number of risk factor exposures by fitting sex-specific models adjusted for age and province. Exposures included in this analysis were having > 4 injections, hemodialysis, blood transfusions, going to the barber, ear or nose piercing, tattoo

or acupuncture, sharing smoking equipment, marriage, illiteracy, and being a laborer.

$$PAF = \frac{P_{\theta}(RR - 1)}{P_{\theta}(RR - 1) + 1} \quad (1)$$

P_{θ} = current prevalence of exposure (e.g., > 4 medical injections)

RR = the adjusted relative risk of disease due to that specific exposure

In a separate analysis, we investigated the importance of childbirth for HCV acquisition in wives aged 20–59 years, adjusting associations for age, province, S-ES, healthcare, and community risk. We did this among married females as only those who are married were assumed to have children in Pakistan.

Sensitivity analyses. As the prevalence of HCV was much higher in the more populated provinces (Punjab and Sindh compared with Baluchistan and North-West Frontier), we performed sensitivity analyses 1) without adjusting for province, 2) omitting Baluchistan and North-West Frontier provinces.

Analyses were conducted, in part, through the National Institute for Health Research Unit (NIHR HPRU) in Evaluation of Interventions (University of Bristol) in partnership with Public Health England.

Statistical analyses were performed in Stata 13.

RESULTS

Overall 2,290/46,843 (4.9% [95% CI: 4.7–5.1%]) of participants had HCV antibodies. The HCV prevalence was 4.8% (4.6–5.1%) and 4.9% (4.7–5.2%) for females and males, respectively. The prevalence of HCV was 6.7% (6.4–7.0%), 5.1% (4.6–5.5%), 1.1% (0.9–1.3%), and 1.5% (1.2–1.8%) in

Punjab, Sindh, Baluchistan, and the North-West Frontier, respectively.

Association of ungrouped exposures and risk factors with HCV. Table 1 summarizes the exposures associated with HCV stratified by age categories (0–19, 20–29, and ≥ 30 years) and gender, which can be seen in detail in Supplemental Tables 1–3. Prevalence of exposures and association with HCV infection varied by these different categories, with HCV infection rates being higher among married persons (both males and females) compared with persons who were never married, increasing with age, and with community and health-care exposures.

Association of grouped exposures and risk factors with HCV. The HCV prevalence and the unadjusted and adjusted (for age, marital status, province, community, health-care, and S-ES) OR (95% CI) of HCV infection for the community, healthcare, and S-ES grouped exposures are shown in Table 2, separately for males and females. Community, healthcare, and S-ES exposures were all strongly associated with HCV infection. The increase in adjusted odds of prevalent HCV infection associated with one community exposure was similar to that associated with one healthcare exposure. Although the association of HCV infection with multiple healthcare exposures was much stronger than that due to multiple community factors, only a small proportion of the population was exposed to multiple healthcare exposures (females 0.8%; males 0.2%). Older age was associated with HCV infection, with a more than doubling of the rate among males aged ≥ 40 years compared with those aged 20–29 years. Ever (versus never) being married was also associated with HCV infection. Results from the sensitivity analyses—both those excluding provinces with very low prevalence (Supplemental Table 4) and those not adjusting for province (Supplemental Table 5)—were similar to the main analysis, which included all provinces and adjusted for province.

TABLE 1

Variables significantly associated ($P < 0.05$) with hepatitis C virus (HCV) infection, and associated adjusted odds ratios (95% CI) of HCV infection, stratified by age category and gender

Males	OR (95% CI)	Females	OR (95% CI)
Aged 0–19 years			
Barber (vs. not)	1.74 (1.09, 2.78)	Tattoo or acupuncture (vs. not)	12.4 (3.43, 44.5)
Ear or nose piercing (vs. not)	2.67 (1.45, 4.92)	Ear or nose piercing (vs. not)	1.61 (1.20, 2.15)
Laborer (vs. not)	1.96 (1.21, 3.15)	Illiterate (vs. not)	1.62 (1.19, 2.20)
Family history of HCV (vs. not)	2.63 (1.35, 5.15)	Reused syringe (vs. none/new)	1.76 (1.18, 2.63)
Aged 20–29 years			
Barber (vs. not)	1.42 (1.00, 2.00)	Married (vs. never)	1.58 (1.15, 2.19)
Ear or nose piercing (vs. not)	2.21 (1.00, 4.91)	Other marital status (vs. never)	3.77 (1.07, 13.3)
Laborer (vs. not)	1.76 (1.19, 2.60)	Barber (vs. not)	4.22 (1.01, 17.6)
Family history HCV (vs. not)	2.73 (1.42, 5.25)	Tattoo or acupuncture (vs. not)	3.37 (1.04, 11.0)
Aged ≥ 30 years			
Married (vs. never)	1.60 (1.16, 2.22)	Ear or nose piercing (vs. not)	2.30 (1.40, 3.76)
Barber (vs. not)	1.45 (1.24, 1.70)	Family history of HCV (vs. not)	1.95 (1.09, 3.50)
Illiterate (vs. not)	1.30 (1.11, 1.52)	Blood transfusion (vs. never)	5.69 (1.71, 19.0)
Laborer (vs. not)	1.40 (1.18, 1.67)	Illiterate (vs. not)	1.43 (1.15, 1.78)
< 5 injections (vs. 0)	1.71 (1.31, 2.24)	Laborer (vs. not)	2.04 (1.29, 3.20)
5–10 injections (vs. 0)	1.67 (1.25, 2.24)	5–10 injections (vs. 0)	1.64 (1.16, 2.31)
> 10 injections (vs. 0)	2.40 (1.71, 3.37)	> 10 injections (vs. 0)	1.91 (1.31, 2.77)
Reused syringe (vs. none/new)	0.54 (0.44, 0.66)	Reused syringe (vs. none/new)	0.64 (0.51, 0.81)
Unknown syringe type (vs. none/new)	0.42 (0.29, 0.61)	Family history of HCV (vs. not)	2.57 (1.87, 3.53)
Family history of HCV (vs. not)	1.91 (1.38, 2.64)	Hemodialysis (vs. never)	4.37 (1.61, 11.9)
		Blood transfusion (vs. never)	2.49 (1.55, 3.99)

This table summarizes Supplemental Tables 1–3. CI = confidence interval, OR = odds ratio.

TABLE 2

Prevalence of risk factors or exposures and hepatitis C virus (HCV) infection, unadjusted and mutually adjusted odds ratio (95% CI) of HCV infection by sex

Risk Factor	Freq.	HCV Prev.	OR (95% CI) for HCV infection			Adj. P value	Freq.	HCV Prev.	OR (95% CI) for HCV infection			Adj. P value
			Males		Females							
			Unadjusted	Adjusted	Unadjusted				Adjusted			
Never married	15,293	2%	1	1	P = 0.002	12,707	2%	1	1	P < 0.001		
Ever married	9,032	9%	4.14 (3.65, 4.70)	1.43 (1.14, 1.78)		9,811	8%	3.53 (3.07, 4.06)	1.54 (1.23, 1.94)			
Community risks 0	17,306	3%	1	1	P = 0.006	6,796	3%	1	1	P = 0.005		
Community risks 1	6,105	9%	2.73 (2.41, 3.10)	1.22 (1.06, 1.41)		15,492	6%	2.18 (1.85, 2.58)	1.46 (1.21, 1.76)			
Community risks ≥ 2	914	12%	4.10 (3.30, 5.10)	1.34 (1.06, 1.69)	P = 0.013	230	10%	3.82 (2.41, 6.07)	2.07 (1.25, 3.44)	P = 0.001		
S-ES risks 0	14,166	4%	1	1	P < 0.001	10,389	3%	1	1	P < 0.001		
S-ES risks ≥ 1	10,159	7%	1.84 (1.64, 2.07)	1.33 (1.17, 1.51)		12,129	6%	2.00 (1.75, 2.30)	1.55 (1.33, 1.81)			
Healthcare risks 0	17,570	4%	1	1	P = 0.005	15,660	4%	1	1	P < 0.001		
Healthcare risks 1	6,701	6%	1.45 (1.28, 1.65)	1.21 (1.06, 1.39)		6,675	7%	1.75 (1.54, 1.99)	1.40 (1.22, 1.61)			
Healthcare risks ≥ 2	54	20%	5.57 (2.86, 10.83)	3.31 (1.69, 6.47)	P < 0.001	183	22%	7.16 (5.00, 10.26)	4.17 (2.84, 6.14)	P < 0.001		
Punjab (Province)	13,186	7%	1	1	P < 0.001	11,926	7%	1	1	P < 0.001		
Sindh	4,640	5%	0.73 (0.63, 0.86)	0.69 (0.59, 0.82)		4,221	5%	0.75 (0.64, 0.89)	0.67 (0.56, 0.79)			
Baluchistan	3,831	1%	0.15 (0.11, 0.22)	0.16 (0.11, 0.22)	P < 0.001	3,766	1%	0.16 (0.11, 0.22)	0.14 (0.10, 0.19)	P < 0.001		
North-West Frontier	2,668	1%	0.18 (0.13, 0.27)	0.19 (0.13, 0.28)	P < 0.001	2,605	2%	0.24 (0.17, 0.33)	0.20 (0.14, 0.29)	P < 0.001		
Age 0–9	5,309	2%	0.36 (0.27, 0.49)	0.48 (0.35, 0.66)	P < 0.001	5,013	2%	0.39 (0.30, 0.50)	0.63 (0.46, 0.85)	P = 0.003		
Age 10–19	6,360	2%	0.59 (0.47, 0.74)	0.77 (0.60, 0.99)	P = 0.041	5,808	2%	0.48 (0.38, 0.60)	0.69 (0.53, 0.89)	P = 0.005		
Age 20–29	4,420	4%	1	1	P < 0.001	4,272	5%	1	1	P < 0.001		
Age 30–39	2,831	7%	1.90 (1.54, 2.34)	1.53 (1.20, 1.95)		2,910	8%	1.84 (1.52, 2.23)	1.47 (1.20, 1.81)			
Age 40–49	2,292	11%	3.17 (2.60, 3.88)	2.43 (1.90, 3.09)	P < 0.001	2,109	9%	1.88 (1.54, 2.31)	1.40 (1.12, 1.75)	P = 0.003		
Age 50–59	1,479	11%	3.04 (2.43, 3.80)	2.41 (1.85, 3.14)	P < 0.001	1,289	10%	2.20 (1.75, 2.76)	1.55 (1.21, 1.98)	P < 0.001		
Age 60+	1,634	11%	3.06 (2.47, 3.79)	2.22 (1.71, 2.88)	P < 0.001	1,117	9%	1.90 (1.48, 2.43)	1.25 (0.96, 1.63)	P = 0.10		

CI = confidence interval; OR = odds ratio; S-ES = socio-economic status.

A separate analysis where we did not group the exposures that comprised the community, healthcare, and S-ES variables (Supplemental Table 6) shows that a high percentage of those who had had hemodialysis or a blood transfusion had HCV infection but few individuals had undergone these procedures.

PAF of HCV prevalence due to different exposures and risk factors. Most HCV infections were not attributable to an identified risk factor or exposure, although a greater proportion of HCV infections among females, 38% compared with 15% of males, were attributable to either a community or healthcare exposure, with community factors accounting for a greater proportion of HCV infections among both females and males (Figure 1). The PAF suggests that prevention of exposure to community risks could potentially reduce HCV prevalence by 25% (95% CI: 13–35%) and 9% (2–16%) in females and males, respectively. By contrast, prevention of exposure to healthcare risks could potentially reduce HCV prevalence by 13% (8–19%) in females and 6% (2–10%) in males. Among both females and males, a high proportion of HCV appeared to

be attributable to the exposures ever being married (19% and 23%, respectively) and low S-ES (13% and 23%, respectively).

Association of cumulative number of risk factors/exposures with HCV infection. The cumulative number of exposures increased with age, among both females and males (Figure 2). Females accumulated risk factor exposures earlier than males. The prevalence of HCV infection also increased as the number of exposures increased (Figure 3). The HCV prevalence for individuals with 0, 1, 2, 3, 4, and ≥ 5 lifetime exposures was 2%, 3%, 5%, 8%, 11%, and 15%, respectively, with the majority of HCV infections (77%) being among individuals with two or more risk factor exposures. In Punjab and Sindh, the prevalence for individuals with ≥ 5 exposures was 13% and 17%, respectively. The adjusted odds ratio (aOR) of HCV per additional exposure was 1.51 (1.41, 1.61) for females and 1.21 (1.15, 1.27) for males.

Association of childbirth with HCV infection. There were 5,556 married females aged 20–59 years old. There was an increase in HCV infection prevalence associated with

FIGURE 1. Population attributable fraction of hepatitis C virus (HCV) infection due to community and healthcare risks.

the number of children; linear trend, aOR per child 1.06 (1.01, 1.11).

DISCUSSION

Main findings. Our findings identified healthcare-associated exposures, including childbirth, as an important category of risk associated with HCV infection in Pakistan. In addition, our findings also suggest that various community risk factors or exposures, low S-ES, and marriage are

associated with increased risk of HCV infection in the country. We estimate that the risk of HCV infection increases with cumulative lifetime healthcare exposures and accounts for 13% of female and 6% of male infections, whereas community exposures and low S-ES together account for over 20% and 10% of infections in females and males, respectively. Marriage also emerged as an important surrogate marker of risk for both sexes, accounting for about 20% of all prevalent infections; what factors in marriage contribute to HCV infection in Pakistan needs additional study. Unrecognized or

FIGURE 2. Proportion of the population experiencing different numbers of exposures for hepatitis C virus (HCV) infection by age and sex. Exposures included in this analysis were having > 4 injections, hemodialysis, blood transfusions, going to the barber, ear or nose piercing, tattoo or acupuncture, sharing smoking equipment, marriage, illiteracy, and being a laborer.

FIGURE 3. Proportion of population, hepatitis C virus (HCV) prevalence, and proportion of infections among individuals with different numbers of exposures.

unidentified risk factors beyond those associated with marriage, may also play an important role in transmission, as demonstrated by the large proportion of infections not attributable to either community or healthcare exposures identified in this survey. One potential important contributor could be injection drug use, which is a well-documented risk factor for HCV transmission, with injection drug users having a very high prevalence of HCV infection^{17,43–45}; unfortunately, this risk factor was not included in the survey. Alternatively, medical injections may be more important than what our analysis suggests; there was a high prevalence in the population, among both HCV exposed and unexposed individuals, limiting the degree to which we could ascertain the association.

Strengths and limitations. Our study was based on a very large sample size which included children as well as adults. Our results should be generalizable to the population of Pakistan as data were gathered from 100 districts in four provinces. However, the risk factor or exposure questions were limited in scope, often asking whether behaviors had ever occurred, which may have limited the degree to which we could ascribe elevated risk to them. HCV is a chronic condition, thus, infection could have resulted throughout the lifetime of the study subject, further limiting the ability to associate recent exposures with infection. We were unable to determine why marriage and low S-ES were associated with increased prevalence of HCV infection—they may be surrogate markers for risk factors on which we did not have data, or possibly have an effect on healthcare utilization. We also lacked direct data on the number of childbirths among females or where, including home or facility-based deliveries and what type of delivery was performed which limited the scope of our analyses on this risk factor. The survey did not enquire about female genital mutilation or male circumcision, both of which result in parenteral exposures. Our method for measuring the number of childbirths is likely to underestimate the total number as some children would have died or left home; however, it should still be a useful proxy measure for the number of childbirths that a woman has had. It is possible that we may have overestimated the risk associated with community risk factors as accurate attribution of risk to specific medical or healthcare interventions, that are common in the

population, to a chronic infection such as HCV may not reflect the risk of specific exposures.

We used anti-HCV prevalence to determine associations with HCV infection because testing for current HCV infection (e.g., PCR testing for presence of HCV RNA) was not performed. Furthermore, we could not determine acute versus chronic HCV infection; this is a universal problem; very few studies have assessed risk factors for recent, acute, or incident HCV infections amongst the general population.^{9,46–48} This limits the degree to which we can determine current risk factors for HCV transmission as individuals with HCV antibody may have been infected in the distant past or more recently. Importantly, our analysis found similar associations with HCV prevalence in younger and older individuals suggesting similar risk factors may exist now as in the past. One exception was medical injections which was only associated with HCV infection among study subjects aged over 30 years. We cannot determine whether this is because cumulative exposure is more important or there has been a reduction in the risk due to medical injections in recent years.

Comparison with other studies. Our findings are consistent with previous studies examining risk factors for HCV infection^{15,16,43,45,49,50} in Pakistan. In agreement with some studies, we found the importance of healthcare and community exposures for HCV transmission, including medical injections, childbirth, attending barbers and ear or nose piercing.^{15,16,51–57} However, not all studies are in agreement, and some did not find an association with piercing,^{16,17,43,45,49,58} barbering, or medical injections,^{17,43} although these were much smaller surveys. Another study on women in Pakistan found higher S-ES was associated with a higher proportion of injections received using a new syringe, as opposed to reuse. This is one of the possible explanations of the protective association of S-ES on HCV infection that we found and was confirmed in our dataset (results not shown).⁵⁹ This variable could also be a marker of accessing better quality healthcare which could also have a similar effect on reducing HCV risk.

As found in other studies in Pakistan and elsewhere,^{9,12,60–63} marriage is associated with HCV infection for both sexes. The reasons for this are uncertain, with some studies suggesting sexual HCV transmission or shared use of personal items.^{12,63} For females in our study, the dominant exposures included ear and nose piercing, whereas a separate, restricted analysis also found childbirth to be an important exposure, possibly because of parenteral exposures.⁶⁴ For almost every female in Pakistan, ear and nose piercing is a cultural ritual which is undertaken in very early years of life (< 5 years).⁶⁵ Contact with barbers was associated with HCV infection among males. Barbering may be an important risk exposure among children as well as adults as every child (both male and female) undergoes head shaving until 7 days of age.⁶⁵ Also, all male children undergo circumcision, which is mostly carried out by barbers in rural areas, but less so in urban areas.⁶⁶

Importantly, for planning screening interventions, the cumulative number of risk factor exposures reported by an individual was highly predictive of HCV infection, with the seroprevalence of HCV exceeding 10% among individuals with four exposures, and 15% in those with five or more; the effect was even more pronounced, 13% and 17%, respectively, if they were from Punjab or Sindh.

Implications. Our results highlight the importance of HCV prevention interventions not only targeting potential healthcare

risks or exposures in Pakistan but also community settings and family behaviors where exposures may occur. These are likely to include barbering and ear piercing, and family behaviors such as sharing personal items like razors, toothbrushes, glass sharing, and practices associated with childbirth.^{16,45,49,52} More research is needed to better understand the main risk behaviors occurring in different settings. For instance, childbirth may be high risk only in certain settings, or when specific obstetric or gynecological procedures are involved.^{50,52,67} A recent meta-analysis found that caesarean section conferred a high risk for HCV infection (OR = 3.35),¹¹ and other studies have documented the risk of HCV infection to both mother and child after normal labor.^{12,68,69}

A number of educational interventions have been undertaken in Pakistan over the past decade to tackle community and general³⁶ risk exposures such as barbering, tattooing, and body piercing.^{36–38,70} For instance, in 2014/2015, the Health Foundation⁷¹ developed an HCV educational intervention in Karachi, Pakistan, that aimed to educate the general public on healthcare and community risk factors through health educator volunteers and electronic and print media. A similar intervention is being done in Azad Kashmir in Northern Pakistan.⁷² There is a need to better understand the effectiveness and impact of these interventions on practices and HCV transmission.

CONCLUSIONS

In summary, our results highlight the multitude of community and healthcare exposures that drive HCV transmission in Pakistan; similar risk factors for transmission have been identified from Egypt.^{8,9,11,12,73} These findings underscore the urgent need for implementation of strategies to decrease HCV transmission in Pakistan and other countries with similar risk profiles. Treatment scale-up for HCV infection, with the new highly effective direct acting antivirals,^{74,75} is planned in Pakistan, and many are already receiving treatment.⁷⁶ The finding from our study that HCV infection is strongly associated with cumulative number of self-reported risk factors or exposures could help inform screening strategies to efficiently target individuals at highest risk for HCV infection. Although scaling-up treatment is urgently needed to tackle the huge burden of HCV in Pakistan, policy makers should also remember the need for large-scale prevention interventions to curtail the continued transmission of HCV. Indeed, the low prevalence of HCV in many neighboring countries^{77,78} suggests the required changes in behavior should be possible with suitable interventions, including education campaigns, to improve knowledge on HCV transmission risks. These education campaigns need to be tailored to the local situation, which may require further research to identify the reasons why marriage, childbirth, and S-ES are associated with increased HCV risk in Pakistan.

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